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Research Article

Seroepidemiological study of *Herpes simplex virus* 2 in human immuno deficiency virus-positive individuals attending a tertiary care hospital of South India

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ABSTRACT

Background: *Herpes Simplex Virus*-2 (HSV-2) infection is widely studied and associated disease in human immuno deficiency virus-positive (HIV-positive) individuals. The diagnosis of HSV is difficult as the presentations are atypical. Studies have confirmed that HSV-2 infection increases the risk of HIV acquisition by 2-3 folds. The aim of the study was to estimate the seroprevalence of HSV-2 and its association with age, sex and behavioral characters among HIV-infected individuals attending a tertiary care hospital.
Methods: Serum samples from 150 HIV positive patients were collected and screened for HSV-2 Ig G antibodies by indirect ELISA. The cut off index (COI) of each serum sample was determined by dividing the OD which was obtained for that serum sample, by the average OD of the cutoff serum. A COI below or equal to 1 was considered as negative and that above 1.1 was considered as positive.
Results: The overall seroprevalence of HSV-2 in the study was 44% (95% CI: 36-52%) with more in men than women. Out of 92 men, 42 (45.65%) were HSV positive and 24 (41.38%) of 58 female were positive. Statistical significance was observed in participants who had past history of sexually transmitted disease and who had multiple sexual partners (≥11) making as risk factors for HSV-2 seropositivity. Genital herpes was reported in 41 of 150 participants and seropositivity was 51.22% indicating the lack of awareness and most of the infections are asymptomatic.
Conclusions: Our study demonstrated a clear increase in seroprevalence of HSV-2 in HIV-infected individuals. Findings of our study have relevant public implications and strongly suggest the implementation of interventions in sexually transmitted infections to reduce the prevalence of HSV-2 and associated HIV transmission. As most of the infections of HSV are asymptomatic a continuous program for the screening of HSV in all cases of STD's must be made to reduce the chances of acquisition of HIV and others.

Keywords: Seroprevalence, Herpes simplex virus-2, Human immuno deficiency virus, Sexually transmitted diseases

INTRODUCTION

Human immune deficiency virus (HIV) discovered in the year 1981, has infected millions of people globally. Transmission of HIV and its progression to Acquired immune deficiency syndrome (AIDS) are assisted by many factors with most important are opportunistic infections (OI's).[1] Sexual transmission of HIV is facilitated by the presence of genital ulcer disease. The sexually transmitted infections (STI's) are associated with increased risk of HIV acquisition. Shedding of HIV RNA is 2-3times more in persons with STI's than in normal

individuals.[2] HSV-2 was one of the first OI's to be described in persons with AIDS.[3] Herpes simplex virus 2 (HSV-2) has been studied extensively for its role in HIV acquisition, transmission, and pathogenesis. A shared route of sexual transmission is likely the cause of HSV-2 infection in 50-90% of HIV-infected individuals.[4] However the ulceration that occurs because of HSV-2 in HIV individuals is atypical, severe, persistent and may mimic ulcers of chancroid and syphilis making differentiation difficult.[5] Seroprevalence of HSV-2 in general population ranges from 16.2% in USA, 12% in Australia, 24.4% in Nigeria, and 13.2% in China.[6-9] In India findings of few studies states, the seroprevalence of HSV-2 in the general population ranges from 5.2% to 14.5%.[10-12] Most of the studies state that HSV-2 infection facilitates HIV transmission.[13] HSV-2 seroprevalence in HIV-infected individuals was reported to be 45.8% in Croatia, and 49% in Andhra Pradesh, India.[14,15] A study in Tamilnadu, estimates the seroprevalence of HSV-2 Ig G and Ig M antibodies to be 28.6% and 60% respectively.[16] HIV-induced immune suppression leads to an alteration in the natural progression of the disease. Patients with HIV infection who experience the first or recurrent HSV-2 infections can develop severe and extensive lesions, which may be difficult to treat by standard anti-retroviral therapy. The treatment of HSV infection in HIV-infected individuals suppresses the active HIV replication which occurs during active herpes infection. Few trials demonstrated a clear reduction in genital and plasma HIV replication after three months of treatment with valacyclovir or acyclovir.[17] Treatment of HSV in HIV-infected individuals is challenging because few studies demonstrated a resistance of the virus to acyclovir used commonly.[18]

Therefore seroepidemiological studies are crucial and useful in understanding the distribution and pattern of infection of HSV-2 in populations. Therefore the present study aimed at estimating the Seroprevalence of HSV-2 and its association with age, sex and behavioral characters among HIV-infected individuals attending a tertiary care hospital.

METHODS

The present study was conducted by department of community medicine, Narayana Medical College, Andhra Pradesh, India for a period of six months from January 2015 to June 2015.The study population consisted of all HIV-positive adult patients (Old and newly diagnosed) attending as outpatients of the general medicine and STD department of Narayana general and super specialty hospital. The study group was counseled and informed consent was obtained from all the individuals. All the participants were informed about the confidentiality of their test results and offered treatment if necessary. The demographic data (age, gender, H/O sexual partners etc.) was collected by interviewing the participants and data was entered in a predesigned questionnaire form in MS excel sheet by trained paramedical personnel. A unique numerical code was assigned for each participant to conceal the identity. The study was approved by the institutional ethical and research committee.

Specimen collection and testing: Blood specimens obtained by venipuncture were tested for HSV-2 antibodies. Serum samples were screened for anti-HSV-2 Ig G antibodies by indirect enzyme-linked immunosorbent assay using commercially available ELISA kit. (Novum HSV2 Ig G immunoassay). The kit uses recombinant HSV gG2 antigen to identify HSV-2 antibodies. Positive and negative control serum samples were used in each experiment. The procedure was performed as per manufacturer's instructions. The cut-off value was calculated by dividing optical density (OD) of positive and negative controls. The cutoff index (COI) of each serum sample was determined by dividing the OD which was obtained for that serum sample, by the average OD of the cutoff serum. A COI below or equal to 1 was considered as negative and that above 1.1 was considered as positive.

Data analysis: Data was entered and analyzed using MS excel sheet. Odds ratio and 95% confidence intervals were calculated to measure the association between HSV-2 infection and demographic characteristics and variables. Differences in associations were performed using chi-square test and a p-value less than 0.001 was considered significant.

RESULTS

A total of 150 were included in the study with 92 (61.33%) male, 58 (38.67%) female participants. The mean age of the study group was 40.53 years with male age 40.59 years and female 40.72 years. The predominant age group in the study was 31-45 years with 88 members followed in order by >46 years (36), and least by <30 years (26). 134(89.33%) were positive for HIV-1(male 81 and female 53), 14(9.33%) were HIV-2 positive (male 8 and female 6) and 2(1.33%) were for both HIV-1 and 2 (Male 1 and female 1).

Heterosexual mode of acquisition was commonest (62.67%) followed in order by parenteral route (12.67%) and transfusion (8%), in 16.67% cases, the mode was unknown.

79(52.67%) cases had a history of sexually transmitted disease (STD) and 41(27.33%) had genital herpes and were treated. Of the total 150 cases in the study 22 (14.67%) had a coital debut before 18 years, 42(28%) between 18-20 years and 86 (57.33%) after 21 years. 8.67% (13/150) had more than 11 sexual partners, 58.67% (88/150) had 4 -10 sexual partners and 32.67% (49/150) had less than 3 sexual partners (Table 1).

Table 1: Demographic variables of study population.

Age	No	HSV+ve	HSV-ve
<30 years	26	16 (61.5%)	10 (38.5%)
31 -45 years	88	35 (39.8%)	53 (60.2%)
>46 years	36	16 (41.7%)	20 (58.3%)
Total	150	66 (44%)	84 (66%)
Gender			
Male	92	42 (45.65%)	50 (54.35%)
Female	58	24 (41.38%)	34 (58.62%)
Age of 1st sexual course			
<18years	22	11 (50.0%)	11 (50%)
18 -20 years	42	18 (42.9%)	24 (56.1%)
>21 years	86	37 (43%)	49 (57%)
H/O sexually transmitted disease	79	42 (53.16%)	37 (46.84%)
H/O Genital Herpes	41	21 (51.22%)	20 (48.78%)
No of sexual partners			
<3	49	6 (12.2%)	43(77.8%)
4-10	88	47 (53.4%)	41 (46.6%)
≥ 11 years	13	13 (100%0	0
Mode of HIV acquisition			
Heterosexual	94	43 (45.74%)	51 (54.26%)
unknown	25	12 (48.00%)	13 (52.00%)
transfusion	12	4 (33.33%)	8 (66.67%)
Injection	19	7 (36.84%)	12 (63.16%)
HIV+ve			
HIV-1 +ve	134	52 (38.81%)	82 (61.19%)
HIV-2 +ve	14	12 (85.71%)	2 (14.29%)
Both +ve	2	2	0 (100%)

Table 2: Univariate analysis of risk factors for herpes simplex virus type 2 (HSV-2) infection among human immunodeficiency virus-infected patients.

Characteristic	N	N (%) HSV-2+	O.R. (95% C.I.)	p-value
Gender				
Males	92	42 (45.7%)	1	0.608[a]
Females	58	24 (41.4%)	1.103 (0.755-1.611)	0.609[b]
Age groups (years)				
≤30	26	16 (61.5%)	1	0.138[a]
31 – 45	88	35 (39.8%)	0.646 (0.434-0.962)	0.166[b]
≥ 46	36	15 (41.7%)	0.677 (0.414-1.107)	
Age (years) of first sexual intercourse				
< 18	22	11 (50.0%)	1.162 (0.717-1.885)	0.828[a]
18 – 20	42	18 (42.9%)	0.996 (0.651-1.525)	0.629[b]
≥ 21	86	37 (43.0%)	1	
Lifetime number of sexual partners				
≤ 3	49	6 (12.2%)	1	< 0.0001[a,b]
4-10	88	47 (53.4%)	4.362 (2.010-9.463)	
≥ 11	13	13 (100%)	8.167 (3.859-17.281)	
Mode of HIV acquisition				
Heterosexual	94	43 (45.7%)	0.953 (0.599-1.515)	0.746[a]
Injection	19	7 (36.8%)	0.768 (0.375-1.571)	0.841[b]
Transfusion	12	4 (33.3%)	0.694 (0.283-1.705)	
Unknown	25	12 (48.0%)	1	
Past STD history				
Yes	79	42 (53.2%)	1	0.017[a,b]
No	71	24 (33.8%)	0.636 (0.432-0.935)	
Past history of genital herpes				
Yes	41	21 (51.2%)	1	0.275[a]
No	109	45 (41.3%)	0.806 (0.555-1.171)	0.276[b]

a: Pearson chi-square, b:trend chi-square.

In the study, overall prevalence of HSV-2 Ig G antibodies was 66 (44%) (95% CI:36-52%) with male preponderance of 42 (45.65%) and females 24 (41.38%) and however not statistically significant (p value: 0.608). The highest HSV-2 seropositivity was detected among age group of <30 years (61.5%) followed by >46 years (41.7%). 50% of participants who had coital debut before 18 years, 42.9% who had between 18-20 years and 43% who had after 21 years were seropositive for HSV-2.

53.16% (42/79) who had known history of sexually transmitted disease, 51.22% (21/41) with history of genital herpes were HSV-2 positive. 12.24% (6/49) participants with <3 sexual partners, 53.41% (47/88) with 4-10 partners and 100% (13/13) with ≥11 sexual partners were found to be HSV-2 seropositive (p valve < 0.0001, very highly significant) (Table 2).

Participants of the study with history of sexually transmitted disease were at high risk of acquiring HSV. p valve <0.001, significant 95% CI.

DISCUSSION

In our present study where 150 HIV positive patients were tested for presence of HSV-2 Ig G antibodies, we found that overall seroprevalence was 44%. Findings of our study were in consistent with the findings of Anuradha K et al, Chakraborty N et al and Karad AB who reported a seropositivity of 49%, 47% and 48.4% among HIV positive individuals.[15,18,20] Few of the studies globally reported more seropositivity than in our study with 87% in South Africa and 86% in Uganda.[21,22] However in our study we observed seropositivity of HSV-2 more among the men than in women. This finding is in contrary to the findings of Jacob et al, Anuradha et al who reported more seropositivity among women than men.[23,15] This is explained by more of the participants in the study were men. Studies conducted globally have reported similar and more prevalence of HSV-2 seropositivity ranging from 6% in general population and 50% in high-risk groups.[24] Seroprevalence of HSV in HIV individuals varies widely across regions and from place to place depending on prevalence of HIV. Our study clearly reported a high association of HSV-2 seropositivity in individuals who had coital debut before 18 years which is a highly sexually active age. Similar findings were also reported in the studies of Mertz et al and Santos et al where seropositivity was high in age group of 18 years who had coital debut.[25,26] Most of the infections of HSV were asymptomatic and were not noticed in some due to lack of awareness of genital herpes manifestations. In our study, we observed that HSV seropositivity was clearly high among individuals with multiple sexual partners (>11) which is explained with more number of sexual partners more risk of acquisition of STDs and HIV. A significant association between sexual partners and acquisition of HIV was reported in many studies universally. History of genital herpes was reported in only 27.33% of HIV-positive individuals indicating that only a low proportion of individuals were aware of HSV-2 infections. These findings were in accordance with findings of Santos FC et al, Russel et al and Van benthem et al.[27-29] Prompt diagnosis of HSV-2 infection in HIV individuals leads to patients early management, possible initiation of anti-retro viral treatment leading to reduced shedding of HSV and HIV in genital secretions.[30] Our study supports the findings of Cowan et al that HSV-2 facilitates HIV transmission and strong measures are required for implementation of HSV control measures and development of vaccines against HSV.[31] Our study highlights the need for including HSV-2 testing in HIV-positive individuals to reduce the risk of transmission and genital shedding of virus through herpetic lesions and to identify asymptomatic or unrecognized HSV-2 infections.

The limitations of our study were it was a cross-sectional study with estimation of HSV-2 seropositivity only among HIV-positive patients. This factor limits the general availability of the data with regard to total population.

CONCLUSION

To conclude our study demonstrated a clear increase in Seroprevalence of HSV-2 in HIV-infected individuals. The higher rate of infection could have resulted from different distribution of factors included in our study with high sexual activity. HSV was more in men compared to women and more in age group of <30 years. The study stresses the need for programs for identification of asymptomatic HSV infections in HIV positive individuals. Persons with multiple sexual partners and with coital debut at <18 years of age are more likely to acquire the HSV infection when compared with normal individuals. Statistical significance was associated with risk factors like history of known STD's and other behavioral characters. Findings of our study have relevant public implications and strongly suggest the implementation of interventions in sexually transmitted infections to reduce the prevalence of HSV-2 and associated HIV transmission. As most of the infections of HSV are asymptomatic a continuous program for screening of HSV in all cases of STDs must be made to reduce the chances of acquisition of HIV and others.

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